

**REMARKS/ARGUMENTS**

Subsequent to this amendment, claims 1-4, and 8-11, 14 and 19-21 constitute the pending claims in this application.

Claims 5-7 and 12-13 have been canceled without prejudice, and Applicants reserve the right to reintroduce these or similar claims in this or future patent applications. Applicants note that the Examiner has attached no patentable weight to the functional properties presented in claims 5-7 and 12-13, and accordingly, Applicants maintain that the cancellation of these claims does not represent the surrender of any claim scope.

Claims 15-18 are canceled as being drawn to a non-elected invention. Applicants reserve the right to pursue any of the withdrawn claims in future applications.

Claims 19-21 have been added. Support for these new claims can be found, for example, in Example 8 at page 46 and in the paragraph bridging pages 24 and 25.

Claims 1, 4, 9, 10 and 11 have been amended solely to correct grammatical inconsistencies and to clarify the claim language. Applicants do not believe that the amendments represent any change in scope of the claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

No new matter is introduced in any of the above amendments.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

**Claim rejections under 35 U.S.C. 103(a)**

The Examiner has rejected claims 1-14 as being allegedly obvious over Uchida et al. (U.S. 6,150,092) in view of Robinson et al. (WO 95/04142), Agrawal et al. (PNAS, 94:2620-2625, 1997), and Bennett et al. (U.S. 5,998,148).

Specifically, the Office Action asserts that, “[t]he antisense oligonucleotides claimed by Uchida et al. are targeted, for example, to the specific region of VEGF nucleic acid SEQ ID NO: 7. It is noted that antisense oligonucleotides of the instant application, including claimed SEQ ID NO: 34 (modified version of SEQ ID NO: 2) as well as SEQ ID NOS: 2, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 28, and 29, for example, are all targeted to SEQ ID NO:7 of Uchida et al, and further all the antisense oligonucleotides of the instant application either overlap, embrace, or are embraced by the specifically claimed antisense of Uchida et al claim 7, for example (SEQ ID NOS: 51, 54, 53, 50, 49, 138, and 141 of Uchida et al, for example).” See Office Action, the paragraph bridging pages 3 and 4.

Further, the Examiner admits that Uchida et al. do not disclose the 2’ O-methyl modifications of SEQ ID NO: 34, the specific cells of claim 7, combinations with chemotherapeutic agents or the use of liposomes. However, the Examiner alleges that the 2’ O-methyl modifications are disclosed by Robinson et al., and that Agrawal et al. have taught the same modification used in SEQ ID NO: 34. The Examiner also asserts that Bennett et al. teach many modifications as well as liposome delivery.

Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended. Applicants submit that the pending claims as amended are drawn to a specific oligonucleotide wherein the specific oligonucleotide is modified to comprise a plurality of phosphorothioate (PS) moieties.

Applicants maintain, for the reasons already made of record as well as the reasons presented below, that the claimed oligonucleotides and methods are not obvious in view of the cited art.

**1. The cited references fail to teach each and every limitation of the claimed invention.**

Although certain of Applicants’ sequences fall within the region defined by Uchida’s SEQ ID NO: 7, Uchida et al. do not disclose the exact nucleic acid (e.g., SEQ ID NO: 34), either as modified in SEQ ID NO:34 or in the unmodified form, as in SEQ ID NO:2. In addition, Uchida et al. do not disclose the modified form of the exact nucleic acid which comprises 2’O-methyl modifications, as recited in claims 1 and 8. Applicants submit that none of Robinson et

al., Agrawal et al., and Bennett et al. can overcome the deficiencies of Uchida et al. Therefore, the proposed combination of these cited prior art references fails to teach each and every limitation of the claimed invention.

The Examiner has relied on Agrawal et al. in order to provide the teaching of 2'O-methyl modified antisense nucleic acids as combined with Uchida et al. in order to arrive at the presently claimed nucleic acids. However, it is Applicant's position that one of ordinary skill in the art would not have, upon review of the cited documents, and particularly Uchida et al., been motivated to make any 2'O-methyl or phosphorothioate modified versions of the antisense probes disclosed by Uchida et al.

**2. The cited references fail to provide sufficient motivation for a skilled artisan to develop the claimed invention.**

MPEP 2142 sets forth criteria that must be met in order to establish a prima facie case of obviousness. These criteria include the requirement that there must be some motivation for one of ordinary skill in the art to modify the prior art reference to arrive at Applicants' invention.

It is Applicants' position that the Examiner has failed to make a prima facie case for obviousness because Uchida et al. do not provide any motivation for one of ordinary skill in the art to make the 2'O-methyl or phosphorothioate modified antisense probes claimed in the present application. Moreover, the motivation cannot be found in any of the other cited references.

In order to arrive at the presently claimed invention, one of ordinary skill in the art would need to change the sequence of one of the antisense probes described in Uchida et al. and, further, introduce 2'O-methyl modifications. Uchida et al. disclose unmodified antisense probes that are effective in decreasing VEGF expression in cell-free assays (see, e.g., Uchida et al., Tables 1-8). However, as noted in the Declaration under 37 CFR 1.132 from Dr. Gill, 2'O-methyl modifications and/or phosphorothioate modifications are employed only when an antisense probe is intended for use in cells. Therefore, the unmodified probes described by Uchida et al. would not render obvious the claimed phosphorothioate- and 2'O-methyl-modified probes unless there were some evidence that such modified probes would be effective in cells.

Although Uchida et al. briefly describe cell-based assays with PS-modified forms of antisense probes, these PS-modified probed did not work well in cells. For example, Table 9 of

Uchida et al. clearly shows that the amount of VEGF expression in the presence of the PS-modified probes remained high, ranging from 54% to 70% of normal (59% to 82% when corrected for the baseline inhibition seen in the controls).

The ineffectiveness of the probes described in Uchida et al. to affect VEGF expression in cells is further substantiated by the Declaration from Dr. Gill, noting that the cell-based assays were performed at an exceptionally high concentration of phosphorothioate-modified probe. While the cell-free assays were performed with 0.4 micromolar concentrations of antisense nucleic acids, the cell-based assays were performed at a 50-fold higher concentration of 20 micromolar. According to Dr. Gill, the concentration of 20 micromolar is so high as to create non-specific results in many instances. And yet, despite the high concentration, none of the six phosphorothioate-modified probes tested by Uchida et al. had a strong effect on VEGF expression in cells.

Furthermore, unmodified probes that were highly effective for inhibiting VEGF expression in the cell-free assay were, after phosphorothioate modification, poorly effective in the cell-based assays. As noted by Dr. Gill, the A311 probe (SEQ ID NO: 51 in Uchida et al.) inhibited 96% of VEGF expression in the cell-free assay, but only inhibited 22% to 28% of VEGF expression in cells (and at a 50-fold higher concentration). Dr. Gill concludes from this discrepancy that the cell-free assay performed by Uchida et al. is a poor predictor of phosphorothioate modified probes that will be effective in cells.

Accordingly, Uchida et al. does not provide one of ordinary skill in the art with the motivation to use any of the disclosed antisense probes in an in vivo or cell-based setting. Therefore, one of ordinary motivation would not have any motivation to create modified forms of such probes using modifications that are designed for use in vivo. Having seen from Uchida et al. that six out of six probes identified through the cell-free assay were poorly effective in the cell based assay, one of ordinary skill in the art would not be motivated to modify any of the other probes disclosed therein with 2'O-methyl modifications or phosphorothioate modifications for use in cells.

To conclude, one of ordinary skill in the art would appreciate that Uchida et al. provide no meaningful guidance for the selection of antisense probes for use in cells. Given that SEQ ID NO: 34, either unmodified or modified, is not disclosed literally in Uchida et al., it is

unreasonable to assume that one of ordinary skill in the art could find in the teachings of Uchida et al. any motivation to make those particular sequences and to further modify these oligonucleotides with phosphorothioate moieties and 2'O-methyl ribonucleotides. In addition, no other reference cited provides any sequence that is identical or similar to SEQ ID NO: 34, let alone the phosphorothioate- and 2'O-methyl-modified forms of this oligonucleotide.

Accordingly, Applicants submit that all of the pending claims are non-obvious in view of Uchida et al. Furthermore, since none of the defects of Uchida et al. are cured by the other cited references, Applicants assert that the claims are not obvious in view of all cited references. Applicants respectfully request reconsideration and withdrawal of the rejection of the pending claims under 35 USC § 103.

### **CONCLUSION**


For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945**. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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